ARTICLES

Mortality From Second Tumors Among Long-Term Survivors of Retinoblastoma

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Background: **Children diagnosed with retinoblastoma, a rare cancer of the eye, tend to develop and die of second primary cancers in childhood and adolescence, but few investigations have followed patients into adulthood. Retinoblastoma is frequently caused by inherited mutations of the RB1 tumor suppressor gene. Most patients with germline (hereditary) mutations have bilateral disease.** ***Purpose:*** **We sought to quantify the mortality from second malignancies among long-term survivors of retinoblastoma and to identify factors that predispose to these deaths.** ***Methods:*** **A retrospective cohort study examined mortality among 1603 patients enrolled at 1 year after diagnosis of retinoblastoma during the period 1914-1984. Data on demography, family history, and retinoblastoma treatment were collected by medical chart review and questionnaire interview. Number of deaths, by cause, was compared with the corresponding expected figure based on U.S. mortality data for the general population for 1925-1990.** ***Results:*** **Follow-up was complete for 1458 patients (91%) for a median of 17 years after retinoblastoma diagnosis. A total of 305 deaths occurred, 167 of them from retinoblastoma. There were 96 deaths from second primary tumors (relative risk [RR] = 30), 21 from other known causes (RR = 1.0), and 21 from ill-defined or unknown causes. Statistically significant excess mortality was found for second primary cancers of bone, connective tissue, and malignant melanoma and benign and malignant neoplasms of brain and meninges. Among 919 children with bilateral retinoblastoma, 90 deaths from second primary tumors occurred (RR = 60). Deaths from second tumors were more frequent among females (RR = 39) than males (RR = 22) (*P* = .007). The cumulative probability of death from second primary neoplasms was 26% at 40 years after bilateral retinoblastoma diagnosis, and additional cancer deaths occurred thereafter. Radiotherapy for retinoblastoma further increased the risk of mortality from second neoplasms. An excess of mortality from a second cancer, not seen in prior studies, was found among the 684 children with unilateral disease (RR = 3.1; 95% confidence interval = 1.0-7.3).** ***Conclusions:*** **These findings implicate germinal mutations in the retinoblastoma gene in second cancer mortality. Radiotherapy treatment for retinoblastoma appears to further enhance the inborn susceptibility to development of a second cancer.** ***Implications:*** **Patients with retinoblastoma, particularly bilateral retinoblastoma, should have careful follow-up, and interventions should be developed to reduce mortality from a second cancer. [J Natl Cancer Inst 85:1121-1128, 1993]**

Retinoblastoma, a rare cancer of the eye that develops predominantly in children under the age of 4 years, is the prototype of hereditary cancers in humans *(1-5).* Approximately 30%-40% of retinoblastoma cases, including all bilateral cases, can be transmitted in an autosomal dominant pattern with 90% penetrance (i.e., 90% of the carriers of this gene develop retinoblastoma) *(6).* Studies of familial retinoblastoma *(2,4)* yielded Knudson's two-mutation model of tumorigenesis. The model specifies that familial retinoblastoma is due to a germline mutation and a subsequent somatic mutation. In contrast, sporadic retinoblastoma results from two somatic mutations. The retinoblastoma gene (RB1) was localized to the long arm of chromosome 13q14 in a few retinoblastoma patients with congenital anomalies who also had interstitial deletion of chromosome 13q14 *(7-9).* In 1986, RB1 was the first of the tumor suppressor genes to be cloned *(10).* Subsequent studies *(10-20)* have shown somatic mutations of RB1 in a variety of cancers, including sarcomas, breast cancer, lung cancer, and genitourinary cancers.

Retinoblastoma is curable in most patients *(21,22).* However, hereditary retinoblastoma patients, approximately

*See "Notes" section following "References."

80% of whom have bilateral disease, are at high risk of developing and dying of second primary cancers in childhood and adolescence *(22-41)*. In the current study, we sought to quantify the mortality from second malignancies among long-term survivors of retinoblastoma and to identify factors that predispose to these deaths among 1603 retinoblastoma patients who had follow-up for up to 70 years.

Materials and Methods

Study Population

The study series comprised retinoblastoma patients who were seen at medical centers in New York and Boston and who had survived at least 1 year after initial diagnosis. A total of 1730 patients were identified from medical records at the Columbia Presbyterian Hospital (1914-1979). New York Hospital–Cornell Medical Center (1980-1984) (both in New York, N.Y.), and four Boston medical institutions (Massachusetts Eye and Ear Infirmary, Boston Children's Hospital, Dana-Farber Cancer Institute, and Massachusetts General Hospital [1937-1984]). The study group consisted of 1603 patients. Of the remaining 127 patients who were excluded from further study, 112 died within 12 months of diagnosis, 11 died outside the United States, and four died prior to 1925. Hospital records and clinic charts of the 1603 study patients were abstracted for demographic and follow-up data, tumor laterality, disease extent and treatments administered, occurrence of a second primary neoplasm, family history of retinoblastoma, and dates and causes of death for decedents.

Most patients treated in New York had been evaluated preciously for second cancers and mortality *(25,27,28,30,31,34,40)*. The current study differs in design from these prior reports in that follow-up was longer and more complete, and late mortality among long-term survivors of retinoblastoma was the prime focus. Extensive efforts were made to trace and contact all patients, conduct questionnaire interviews, and document relevant end points.

Follow-up Procedures

Contact with most patients was established through the last available address and telephone number in the medical record. For patients who had moved, current telephone numbers and addresses were sought through the postal service, local telephone directories, state motor vehicle regulations, and credit bureaus. Other sources for location included the patients' next of kin listed in medical records, patients' neighbors, schools or religious organizations, telephone directory assistance, and voter registration boards.

After the patient (or family member in some cases) was located, consent was obtained to conduct a standardized interiew. Information was gathered on current health, occurrence of a second tumor, and family history of retinoblastoma. Interviews were completed for 1064 of the 1153 patients found to be alive. In addition to the sources listed ahove, deaths were identified by linkage with computer tapes of the National Death Index, 1979-1990, and the Social Security Administration, 1965-1990. Death certificates were requested from state departments of vital statistics, and causes of death were coded by trained nosologists according to the International Classification of Diseases, 8th revision (ICD8), which classifies tumors according to site rather than histology *(42)*. Supplementary medical records and pathology reports also were collected on patients who died of cancer.

Analysis and Statistical Methods

The numbers and rates of deaths, by cause, among study patients were calculated and compared with expected figures based on U.S. mortality data, 1925-1990 *(43)*. Adjustments were made for age, sex, and calendar year. For most patients, the period of observation began 1 year after the diagnosis of retinoblastoma. For the few children diagnosed prior to 1925, the beginning date for follow-up was set to 1925, which was the first year that U.S. mortality rates were readily available. The end of the period of risk was taken as the date of death for those who died or the last date that the patient was known to be alive. Patients known to be alive after January 1, 1979, and not found to be listed on the National Death Index, which was searched from 1979 through 1990, were considered to be alive as of December 31, 1990.

Mortality was examined among the entire series and by subgroups defined on the basis of tumor laterality, age at diagnosis, sex, study center (Boston versus New York), and retinoblastoma treatment with radiation. Chemotherapy data were incomplete or unavailable and considered inassessable. The relative risk (RR) of mortality was estimated as the ratio of observed to expected deaths, and 95% confidence intervals (CIs) were calculated assuming a Poisson distribution. The absolute excess risk was estimated as the difference between the observed and expected deaths divided by the person-years of observation. Kaplan–Meier plots *(44)* of the cumulative probability of death from a second tumor were obtained assuming no deaths from second neoplasms within 1 year of diagnosis of retinoblastoma.

Results

Characteristics of the 1603 eligible subjects are shown in Table 1. Unilateral retinoblastoma was diagnosed in 684 (43%) patients and bilateral retinoblastoma in 919 (57%). The high percentage of bilateral cases reflects the selective referral of such patients to the study centers. As expected, approximately 90% of patients were diagnosed with retinoblastoma before 3 years of age, and patients with bilateral disease tended to be younger at diagnosis than those with unilateral disease *(6,22)*. Approximately 30% of patients were diagnosed with retinoblastoma prior to 1960. The median age of the cohort at last follow-up was 20 years (range, 1-72 years). The major racial groups in the United States appeared to be proportionately represented in the study series. A family history of retinoblastoma was reported for 249 patients (16%), including 44 with unilateral disease. Radiotherapy, with or without chemotherapy, was given to 965 patients (60%).

Overall, 1458 (91%) of the subjects with retinoblastoma were located: 1153 were found to be alive, 305 had died, and the remaining 145 were lost to follow-up. The inability to locate subjects was almost entirely due to sketchy medical records that contained little identifying information. Subjects lost to follow-up, however, were similar to those located in terms of age at diagnosis, sex, laterality, and treatment, but they tended to have been diagnosed earlier, i.e., prior to 1960. The median follow-up after retinoblastoma diagnosis was 17 years, and 724 patients contributed 6719 person-years of follow-up beyond 20 years of observation. Retinoblastoma was the cause of 167 deaths. There were 143 deaths due to retinoblastoma between 1 and 9 years after initial diagnosis, 19 deaths in the next decade, and five deaths thereafter. These figures confirm the rarity of late mortality attributable to retinoblastoma *(22,31)*.

The 138 deaths from causes other than retinoblastoma exceeded the 23.1 deaths expected (RR = 6; 95% CI = 5.0-7.0) (Table 2). The excess was primarily caused by 96 deaths from second tumors (RR = 30), both malignant and benign. High RRs that exceeded 300-fold were found for malignant neoplasms of bone and connective or soft tissue. Death due to melanoma exceeded expectation by nearly 100-fold and death due to brain cancer by 24-fold. Twenty cancers of other sites were also excessive (R R = 8); among

Table 1. Charcteristics of 1603 retinoblastoma patients who were alive 1 year after diagnosis, by tumor laterality*

Characteristic	Unilateral Rb (%)	Bilateral Rb (%)	Total (%)
No. of subjects	684 (100)	919 (100)	1603 (100)
Study center			
New York	547 (80)	847 (92)	1394 (87)
Boston	133 (19)	66 (7)	199 (12)
Both	4 (1)	6 (<1)	10 (<1)
Sex			
Male	356 (52)	492 (54)	848 (53)
Female	328 (48)	427 (46)	755 (47)
Age at Rb diagnosis, y			
<1	163 (24)	522 (57)	685 (43)
1	208 (30)	260 (28)	468 (29)
2	163 (24)	103 (11)	266 (16)
3-17	150 (22)	34 (4)	184 (11)
Year of Rb diagnosis			
1914-1949	78 (11)	103 (11)	181 (11)
1950-1959	104 (15)	195 (21)	299 (19)
1960-1969	213 (31)	296 (32)	509 (32)
1970-1979	204 (30)	241 (26)	445 (28)
1980-1984	85 (12)	84 (9)	169 (10)
Age at last observation, y			
1-9	131 (19)	237 (26)	364 (23)
10-19	186 (27)	236 (26)	422 (26)
20-39	313 (46)	394 (43)	707 (44)
40-72	58 (8)	52 (6)	110 (7)
Family history of Rb			
Yes	44 (6)	205 (22)	249 (16)
No or unknown	640 (94)	714 (78)	1354 (84)
Treatments reported			
Radiation only	80 (12)	454 (49)	534 (33)
Chemotherapy only	41 (6)	12 (1)	53 (3)
Both	50 (7)	381 (41)	431 (27)
Neither	505 (74)	66 (7)	571 (36)
Therapy uncertain	8 (1)	6 (<1)	14 (<1)

* Rb = retinoblastoma. Percentages may not add up to 100 due to rounding

them were five sarcomas of the kidney, colon, respiratory system, ovary, and uterus. The five sarcomas of visceral organs and 51 sarcomas of bone and connective tissue account for 63% (56/89) of all second cancer deaths. There was one death due to acute lymphoblastic leukemia previously reported *(34)* among the 965 irradiated patients and another due to alveolar adenocarcinoma of the thyroid. The seven deaths from benign tumors, most arising in brain and meninges, were also excessive (RR = 57).

There were no deaths coded to the rubric for pinealoblastoma, which has also been called "trilateral retinoblastoma'" *(45)*. Interestingly, pinealoblastoma had developed in five patients who later died; however, the cause of death was recorded as retinoblastoma in three cases and malignant neoplasm of brain and contusion in the other two. Because the current study compares mortality among retinoblastoma patients to that expected in the general population, cause of death was based solely on death certificate codes.

There were 21 deaths due to nonneoplastic causes and 21 due to unknown conditions: 10 were coded as ill-defined conditions, and 11 death certificates could not be obtained. For the 21 patients with specified causes of death, the observed distribution was consistent with expectation (RR = 1). No excess deaths from accidents or suicides occurred among these visually impaired retinoblastoma patients (RR = 0.7).

Analysis of temporal trends in mortality from second neoplasms revealed that rates were significantly elevated during all intervals of follow-up, even beyond 40 years (Table 3). The absolute excess risk increased significantly with time after diagnosis, from 1.5 deaths per 1000 persons per year at 1-9 years of follow-up to 12.7 deaths per 1000 persons per year after 40 years of follow-up. The RR increased during the first 20 years after retinoblastoma diagnosis. The subsequent decline in the RR reflects an increasing baseline cancer mortality rate with age. Time trends for specific neoplasms were hard to distinguish because of small numbers. Deaths due to bone and connective tissue tumors occurred throughout the first 4 decades of follow-up, brain tumors tended to occur early, and melanoma and other cancers appeared to occur later.

Mortality from second tumors was examined by retinoblastoma laterality (unilateral or bilateral) and radiotherapy (Table 4). The RR was much higher among patients with bilateral retinoblastoma (90 deaths, RR = 60; 95% CI = 45.9-70.2) than with unilateral disease (six deaths, RR = 3.8; 95% CI = 1.4-8.2). All 51 deaths due to cancers of the bone and connective tissue developed in bilateral retinoblastoma cases; 49 of these patients had received radiotherapy. Children with bilateral disease who received radiotherapy had a nearly threefold higher mortality from second tumors than bilateral nonirradiated patients (RR = 2.9; 95% CI =

Table 2. Causes of death other than retinoblastoma in patients who had been 1-year survivors of retinoblastoma*

Cause of death†	No. of deaths Observed (O)	Expected (E)	O/E
Malignant and benign tumors other than Rb	96	3.2	30‡
Malignant tumors other than Rb	89	3.1	29‡
Bone (170)	36	0.1	325‡
Connective tissue (171)	15	<0.1	423‡
Skin melanoma (172)	9	0.1	94‡
Brain (191-192)	9	0.4	24‡
Other cancers§	20	2.5	8‡
Benign tumors (210-239)‖	7	0.1	57‡
Other known causes of deaths	21	20.0	1
Infections (000-139)	1	0.6	1.6
Neurologic (320-389)	2	0.7	2.9
Cardiac (393-398, 410-414)	3	1.1	2.6
Pulmonary (460-519)	0	0.8	0
Gastrointestinal (520-577)	2	0.7	2.9
Accidents/suicides (800-998)	9	12.8	0.7
Other¶	4	3.3	1.2
Ill-defined condition (796)	10	—	—
No death certificate	11	—	—
All causes other than Rb	138	23.2	6.0‡

* Deaths are those in the United States occurring after 1924. There were 167 retinoblastoma deaths that occurred > 1 year after initial diagnosis. Rb = retinoblastoma.

† Values in parentheses indicate cause of death according to International Classification of Diseases, 8th revision.

‡ P <.05.

§ Other cancers were as follows (numbers in parentheses indicate age at death): one each of cancer of the bladder (65), kidney (6), colon (31), endocrine gland (34), lymphatic leukemia (25), ovary (26), and thyroid (27); two each of nasopharynx (23 and 40), breast (35 and 37), and uterus (34 and 49); three of respiratory system (9, 12, and 12); and four of unspecified site (3, 4, 14, and 45).

‖ Benign tumors were as follows: one each of meningioma of spine, pituitary gland and craniopharyngeal duct, and unspecified organs and tissues; and four of brain.

¶ 0ther known causes of death were as follows: one each of diabetes mellitus, pulmonary embolism and infarction, alcoholism, and drug dependence.

2.2-3.7). There were six unilateral retinoblastoma patients who died of a second tumor, one of whom had a known family history of retinoblastoma.

Unfortunately, information available from death certificates was inadequate to identify tumors that arose within or near the field of irradiation. A comprehensive effort is ongoing to specify precisely the location of each incident sarcoma and to couple this information with detailed dosimetry to estimate actual radiation dose received at the anatomical site where the second cancer developed.

An excess of second cancers was seen in children treated without radiation for bilateral (RR = 22; 95% CI = 7-51) retinoblastoma and in all children with unilateral (RR = 3.1; 95% CI = 1.0-7.3) retinoblastoma. The risk among nonirradiated children with bilateral retinoblastoma was significantly higher than that seen among the children with unilateral disease (P <.02).

Analysis of mortality by sex revealed that females had higher mortality from second tumors (RR = 39) than males (RR = 22) (P = .007). Females were more likely to die of brain cancers and "other cancers" but not of tumors of the bone and connective tissue. The difference persisted after controlling for age at retinoblastoma diagnosis and tumor laterality and radiotherapy and after excluding deaths due to tumors of the breast, ovary, and uterus. In contrast, the mortality from retinoblastoma was similar in both sexes. There was a declining probability of mortality from nonocular cancers with increasing age at retinoblastoma diagnosis (P <.001). The apparent age effect, however, may be due to radiotherapy doses that tended to be higher among children under the age of 1 in our study.

At 40 years of follow-up, the cumulative mortality for all second neoplasms combined was 26.0% ± 3.9% (expected, 1.3%; P <.05) for the bilateral group and 1.5% ± 0.7% (expected, 1.1%; P >.05) for the unilateral group (Fig. 1). Among the bilateral retinoblastoma patients, cumulative

Table 3. Mortality from tumors other than retinoblastoma in patients who had been 1-year survivors of retinoblastoma, by duration of follow-up*

	Observed (O) and expected (E) No. of deaths by years after Rb diagnosis											
	1-9			10-19			20-39			≥40		
No. of persons followed up†	1602			1187			724			79		
Person-years	12383			9594			6719			562		
Cause of death	O	E	O/E	O	E	O/E	O	E	O/E	O	E	O/E
Malignant tumors other than Rb	19	0.7	26‡	37	0.5	69‡	26	1.0	26‡	7	0.9	8‡
Bone	7	<0.1	240‡	21	<0.1	360‡	8	<0.1	390‡	0	<0.1	0
Connective tissue	2	<0.1	150‡	9	<0.1	800‡	2	<0.1	220‡	2	<0.1	1000‡
Skin melanoma	1	<0.1	1000‡	1	<0.1	100‡	6	<0.1	93‡	1	<0.1	51
Brain	5	0.2	30‡	3	<0.1	35‡	0	<0.1	0	1	<0.1	33
Other cancers	4	0.5	8‡	3	0.4	8‡	10	0.8	12‡	3	0.8	4
Benign tumors	0	<0.1	0	5	<0.1	160‡	1	<0.1	32	1	<0.1	100‡
All tumors other than Rb	19	0.7	26‡	42	0.5	78‡	27	1.0	27‡	8	0.9	9‡
Excess risk per 1000 person-years		1.5			4.3			3.9			12.7	

* Deaths are those in the United States occurring after 1924. Rb = retinoblastoma.

† An individual whose follow-up began before 1925 is excluded in the 1-9 years interval because he or she was not at risk of dying during that period.

‡ P <.05.

Table 4. Mortality from tumors other than retinoblastoma in patients who had been 1-year survivors of retinoblastoma, by laterality and irradiation status*

	Observed (O) and expected (E) No. of deaths and O/E ratios											
	Bilateral						Unilateral					
	Irradiated (N = 835)			Nonirradiated (N = 84)			Irradiated (N = 130)			Nonirradiated (N = 554)		
Cause of death	O	E	O/E	O	E	O/E	O	E	O/E	O	E	O/E
Malignant tumors other than Rb	79	1.3	61†	5	0.2	22†	2	0.4	5	3	1.2	2
Bone	34	<0.1	630†	2	<0.1	270†	0	<0.1	0	0	<0.1	0
Connective tissue	15	<0.1	880†	0	<0.1	0	0	<0.1	0	0	<0.1	0
Skin melanoma	7	<0.1	180†	1	<0.1	120†	0	<0.1	0	1	<0.1	25
Brain	8	0.2	45†	0	<0.1	0	0	<0.1	0	1	0.1	7
Other cancers	15	1.0	15†	2	0.2	11†	2	0.4	5	1	0.9	1
Benign tumors	6	<0.1	100†	0	<0.1	0	0	<0.1	0	1	<0.1	22
All tumors other than Rb	85	1.3	63†	5	0.2	22†	2	0.4	5	4	1.2	3
Excess risk per 1000 person-years		5.8			2.5			0.8			0.2	

* Deaths are those in the United States occurring after 1924. Rb = retinoblastoma.
† $P < .05$.

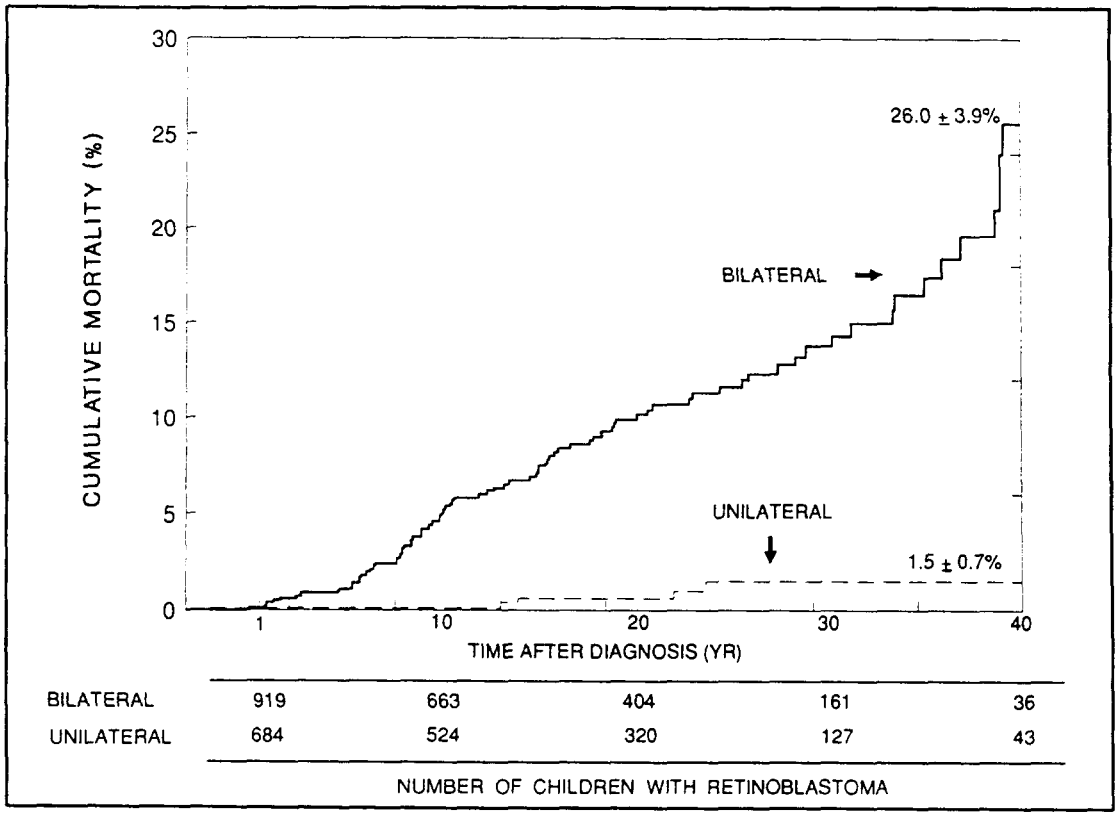

Fig. 1. Cumulative mortality from second primary neoplasms during follow-up of the entire cohort of 1603 retinoblastoma patients by laterality (bilateral and unilateral).

mortality from second primary neoplasms at 40 years of follow-up was higher among patients who received radiotherapy (30.3% ± 4.8%) than for those who did not (6.4% ± 3.89%) (Fig. 2).

Discussion

Excess mortality from second cancers in retinoblastoma survivors was found to persist during long-term follow-up into adulthood. A large series of 1603 patients was assembled from medical centers in New York and Boston. and extensive tracing efforts located 91% of them. Patients with bilateral retinoblastoma had high death rates from nonocular cancers, particularly tumors of bone, connective tissue, and brain and malignant melanoma. The excess mortality from second cancers continued unabated into adult life, reaching almost 13 extra deaths per 1000 persons per year beyond 40 years of observation. The second cancer mortality rate at 40 years of follow-up among bilateral retinoblastoma patients (26%) has already equaled the expected lifetime cumulative mortality from all cancers combined in the general population *(46)*. The rate was

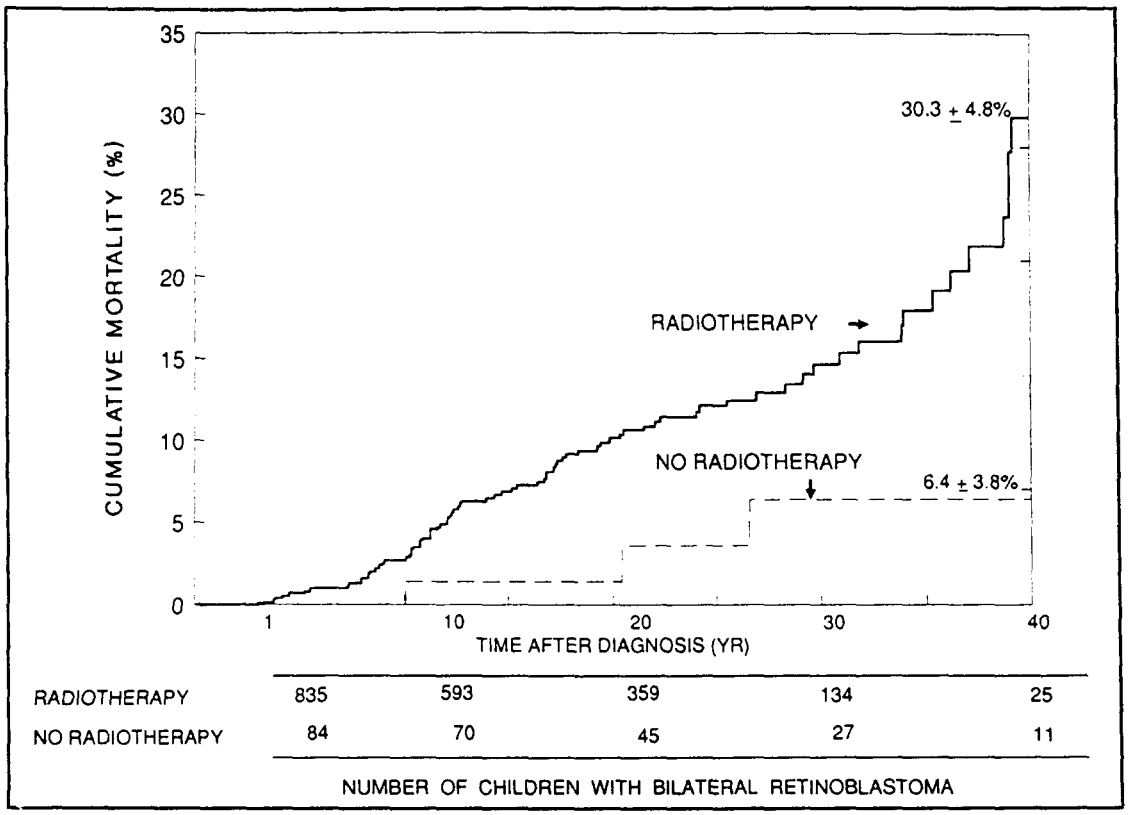

Fig. 2. Cumulative mortality from second primary neoplasms during follow-up of bilateral retinoblastoma patients by treatment with and without irradiation.

further increased among the bilateral patients who received radiotherapy. An excess mortality from second neoplasms observed in the unilateral cases is a new finding which needs to be confirmed. Unexpectedly, females diagnosed with bilateral retinoblastoma had higher mortality from second cancers of the brain and other sites compared with males. The explanation for this difference is uncertain, and additional study is merited.

We found eight other studies *(23,29,33,35,36,38,39,41)* with 50 or more retinoblastoma patients who were evaluated for second cancers. These studies differ substantially in design and population size, with the two largest series including 882 *(23)* and 792 *(41)* retinoblastoma patients. The eight study populations were identified within single institutions *(29,35,41),* multiple centers *(33,39),* or population-based registries *(23,36,38).* The median follow-up ranged from 7 *(33,39)* to approximately 17 years *(35),* and follow-up appeared to be nearly complete in four studies *(23,33,36,38).* Analytical end points included second neoplasm incidence *(23,33,36,38,39,41)* or both incidence and mortality *(29,35).* Three studies *(35,36,39)* were restricted to bilateral or hereditary retinoblastoma, i.e., bilateral plus unilateral with a positive family history. The proportion of patients who received radiotherapy or chemotherapy differed among the series, and treatment doses were rarely specified.

Despite these differences, all eight series *(23,29,33,35,36, 38,39,41)* showed an excess of second tumors in bilateral or all retinoblastoma patients combined. The cumulative risk of second cancer development in bilateral or hereditary retinoblastoma patients tended to cluster around 10% at 20 years of follow-up and 15% at 30 years, usually on the basis of small numbers *(23,29,35,36,41).* The excess tumors in these studies were predominantly bone and soft tissue sarcomas and, in two series *(23,36),* melanomas.

Prior studies may have been too small to detect a significant elevation in second cancer mortality among subjects with unilateral disease. In our series, five of the 684 children with unilateral retinoblastoma developed a nonocular cancer, and the overall risk was significant (RR = 3.1; 95% CI = 1.0-7.3). The increased risk is perhaps not entirely surprising, since a proportion (6%) of the patients with unilateral disease had genetic disease (i.e., as indicated by a family history of retinoblastoma), which placed them at higher risk. Only one of the five children who developed a second cancer, however, was known to have a family history. Even so, it might be that the factors that lead to unilateral rather than bilateral retinoblastoma (variable expressivity) among children with heritable disease also contribute to a lower risk of second tumor development. Interestingly, relatives of retinoblastoma patients, who are themselves affected (i.e., they developed retinoblastoma), have been reported to be at increased risk of cancer that continues into adult life, whereas nonaffected relatives who carry the mutated RB1 gene appear to be at much smaller risk, if any at all *(47).*

Two prior studies *(33,36)* examined the incidence of nonocular cancers in retinoblastoma patients by sex, and no significant difference was found. The Late Effects Study Group *(33)* found a higher but not statistically significant incidence of second cancers among females. In our study, a significantly higher mortality from second cancers was seen among females than among males. Continued follow-up and

combination of published studies might clarify the influence of gender.

Certain features of our study should be considered when interpreting the results. Deaths occurring at less than 1 year after retinoblastoma diagnosis were not examined. The patients were identified at referral centers, where bilateral cases are over-represented. Extensive tracing efforts resulted in a high location rate, and only 9% were lost to follow-up. In addition, interviews were completed with 92% of patients found to be alive. Subgroup analyses were based on relatively small numbers of deaths, even though this is the largest follow-up study to date of retinoblastoma patients. Classification of causes of death might be inaccurate due to difficulties in differentiating retinoblastoma recurrences from second primary tumors *(48)*, although such inaccuracies likely diminish with time. Deaths from second cancers were classified by primary site rather than histology, and the numbers of sarcomas might have been under-represented. Because data were unavailable, the effect of chemotherapy could not be analyzed. However, the absence of an excess of leukemia argues against the possibility that chemotherapy exposures were meaningful. Current treatments for retinoblastoma are different from those in the past and employ megavoltage radiation treatment at generally lower doses. Cancer incidence in our patients was not examined in this study, but this outcome will be the subject of a separate report.

Recent studies have examined the molecular basis of susceptibility to second cancers after bilateral, hereditary retinoblastoma. A germline RB1 mutation in bilateral retinoblastoma patients may lead not only to retinoblastomas of the eye, but also to subsequent sarcomas and carcinomas of various sites. Among patients with retinoblastoma, somatic mutations in the RB1 gene also appear to have a pathogenetic role in a substantial proportion of osteosarcomas and soft tissue sarcomas and carcinomas of the lung, breast, and other sites *(10-20,49)*. Ionizing radiation, which is a known mutagen and carcinogen, might enhance second cancer risk in children with bilateral retinoblastoma by increasing the frequency of somatic mutations needed to produce osteosarcomas, soft tissue sarcomas, and brain tumors *(49-52)*. However, melanomas do not appear to harbor RB1 mutations *(10)* and frequently occur outside radiotherapy sites in retinoblastoma patients *(37)*. Dysplastic nevus syndrome, which predisposes to melanoma, has been reported in some retinoblastoma patients *(37)*. Unfortunately, we were unable to evaluate whether the dysplastic nevus syndrome was present in our patients.

The possibility exists that germline mutations in specific codons or regions of the RB1 gene predispose to the development of second tumors. Point mutations in exon 20 *(53)* or the promoter region *(54)* of the germline RB1 gene have been associated with reduced penetrance. There might also be highly penetrant RB1 mutations that predispose gene carriers to both bilateral retinoblastoma and second cancers. The hypothesis can be tested by searching for clusters of germline mutations within the RB1 gene from patients with bilateral retinoblastoma who develop second cancers.

A small fraction of our patients are over 50 years of age, when cancer incidence rises sharply in the general population. Continued follow-up should reveal whether older survivors of retinoblastoma are prone to other cancers with known RB1 mutations, such as carcinomas of the lung, breast, and ovary. Lifelong clinical surveillance for second cancers is also indicated for patients with retinoblastoma, and the possibility of chemoprevention trials should be considered.

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